
Guidance for Industry

Pharmacokinetics in Patients With Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
November 1999**

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GUIDANCE FOR INDUSTRY¹

PHARMACOKINETICS IN PATIENTS WITH IMPAIRED HEPATIC FUNCTION: STUDY DESIGN, DATA ANALYSIS, AND IMPACT ON DOSING AND LABELING

I. INTRODUCTION

This guidance provides recommendations to sponsors planning to conduct studies to assess the influence of hepatic impairment on the pharmacokinetics (PK) and, where appropriate, the pharmacodynamics (PD) of drugs or therapeutic biologics. This guidance addresses:

- ! When studies are and are not recommended
- ! The design and conduct of studies to characterize the effects of impaired hepatic function on the PK of a drug
- ! Characteristics of patient populations to be studied
- ! Analysis, interpretation, and reporting of the results of the studies and description of the results in labeling

This guidance does not address ways to assess the safety and efficacy of a drug to treat hepatic disease or how to assess whether or not a drug causes hepatotoxicity.

II. BACKGROUND

The liver is involved in the clearance of many drugs through a variety of metabolic pathways and/or through biliary excretion of unchanged drugs or metabolites. Alterations of these excretory and metabolic activities by hepatic impairment can lead to drug accumulation or, less often, to failure to form

¹ This guidance has been prepared by the Hepatic Impairment Working Group in the Clinical Pharmacology Section of the Medical Policy Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration, with contributions from the Center for Biologics Evaluation and Research (CBER). This guidance document represents the Agency's current thinking on this subject. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

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an active metabolite.

Many reports in the biomedical literature have documented that hepatic disease can alter the absorption and disposition of drugs (PK) as well as their efficacious and toxic effects (PD). These reports have been based on studies in patients with common hepatic diseases, such as alcoholic liver disease and chronic infections with hepatitis viruses B and C, as well as less common diseases such as acute hepatitis D or E, primary biliary cirrhosis, primary sclerosing cholangitis, and α_1 -antitrypsin deficiency. Liver disease can alter kidney function, which in turn can lead to accumulation of a drug and its metabolites, even when the liver is not primarily responsible for elimination. Liver disease can also alter PD effects (e.g., increased encephalopathy with certain drugs in patients with hepatic failure). The specific impact of any disease on hepatic function is often poorly described and highly variable, particularly with regard to effects on the PK and PD of a drug.

Measurements such as creatinine or creatinine clearance have been used successfully to adjust dosing regimens for drugs eliminated primarily by the renal route of elimination. Similar measurements of hepatic function have been tried using continuous variables such as bilirubin, albumin, prothrombin time, or marker substrates such as antipyrine, indocyanine green (ICG), monoethylglycine-xylylidide (MEGX) (Testa et al., 1997) and galactose (Tang and Hu 1992). Categorical clinical variables have also been studied. These include ascites or encephalopathy, nutritional status, peripheral edema, histological evidence of fibrosis, or a combination of variables such as the Child-Pugh classification for alcoholic cirrhosis and portal hypertension (Zakim and Boyer 1996, and Pugh et al., 1973), the Mayo risk scores for primary biliary cirrhosis and primary sclerosing cholangitis (Dickson et al., 1989, and Wiesner et al., 1989), and the Maddrey-Carithers discriminant function for acute alcoholic hepatitis (Maddrey et al., 1978, and Carithers et al., 1989) (see Appendix). Despite these extensive efforts, no single measurement or group of measurements has gained sufficiently widespread clinical use to estimate how hepatic impairment will affect the PK and/or PD of a drug in a given patient.

Although clinically useful measurements of hepatic function to predict drug PK and PD are not generally available, clinical studies, usually performed in the investigational phase of drug development in patients with hepatic impairment, provide information that can help guide initial dosing in patients. This information should be used with the understanding that careful observation and dose titration could be necessary to achieve the optimal dose in any given patient.

III. DECIDING WHETHER TO CONDUCT A STUDY IN PATIENTS WITH IMPAIRED HEPATIC FUNCTION

A. When Studies May Be Important

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This guidance recommends a PK study in patients with impaired hepatic function if hepatic metabolism and/or excretion account for a substantial portion of the elimination of a drug or active metabolite. The guidance also recommends a hepatic impairment study, even if the drug and/or metabolite is eliminated through hepatic metabolism and/or excretion to a lesser extent (<20%), if its labeling and/or literature sources suggest that it is a narrow therapeutic range drug,² or if, in the event of renal failure, one or more of the hepatic pathways of elimination could become important. If the metabolism of the drug is unknown and other information is lacking to suggest that hepatic elimination routes are minor, the drug should be considered extensively metabolized.

B. When Studies May Not Be Important

For some drugs, hepatic functional impairment is not likely to alter PK sufficiently to require dosage adjustment. In such cases, a study to confirm the prediction may be helpful but is not necessary. The following drug properties could justify this approach:

- ! The drug is excreted entirely through renal routes of elimination with no involvement of the liver.
- ! The drug is metabolized in the liver to a small extent (<20%) and the therapeutic range of the drug is wide, so that modest impairment of hepatic clearance will not lead to toxicity of the drug directly or by increasing its interaction with other drugs.
- ! The drug is gaseous or volatile and the drug and its active metabolites are primarily eliminated via the lungs.

For drugs intended only for single-dose administration, a hepatic impairment study might not be necessary unless clinical concerns dictate otherwise.

IV. STUDY CONSIDERATIONS

The following sections focus on a *reduced* study design (section A), a basic *full* study design (section B) and a population PK approach (section C).

² The therapeutic index may be derived from the concentration- or dose-response data existing in the safety and/or efficacy database.

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A. Reduced Study Design

1. Study Participants

An FDA survey of 57 PK studies in patients with hepatic impairment for new drug applications (NDAs) submitted between 1995 and 1998 revealed that 55 percent used the Child-Pugh scale to assess hepatic impairment. Nineteen of the 57 studies contained oral drug clearance information in subjects with normal hepatic function and in patients in mild, moderate, or severe Child-Pugh categories. Seventeen of these 19 studies demonstrated a negative correlation (r^2 between 0.5 to 1.0) between oral drug clearance and hepatic impairment, and 16 of 19 demonstrated impaired hepatic metabolism in patients in the moderate Child-Pugh category.

We recommend that the Child-Pugh classification be used to categorize degrees of hepatic impairment, analogous to the use of serum creatinine or creatinine clearance to categorize varying degrees of renal impairment. Other approaches to assess hepatic impairment could be appropriate, but a Child-Pugh categorization should still be included for each patient in the study.

Based on the above data, a reduced study design involving control subjects and patients with a Child-Pugh category of moderate impairment would generally be sufficient. Under these circumstances, the findings in the moderate category will be applied to the mild category and dosing in the severe category would be generally contraindicated (see the Labeling section for details).

A primary goal of this guidance is to provide recommendations on determining whether the PK and/or PD of a drug and its active metabolites are altered to such an extent that the dosage should be adjusted for patients with impaired hepatic function compared to the population for which the drug is intended. For this reason, the control group should represent the patient population with normal hepatic function, not necessarily young healthy volunteers. To the extent possible, the control group should be similar in age, weight, and gender to the hepatically impaired group. Other factors with significant potential to affect the PK of a drug (e.g., diet, smoking, alcohol intake, concomitant medications, ethnicity) should be considered, depending on the drug. For drugs known to exhibit genetic polymorphism (e.g., CYP4502D6 or CYP4502C19), the sponsor should consider the metabolic status of the enrolled subjects when analyzing the results of the study. In addition to standard clinical tests performed prior to entry, sponsors may wish to perform assessments of hepatic blood flow or intrinsic clearance using

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markers such as ICG, antipyrine, MEGX, or galactose. A sufficient number of subjects should be enrolled in the study such that evaluable data can be obtained from at least eight subjects in each arm of the study.

2. Drug Administration

A clinical study to investigate the effects of hepatic impairment on drug disposition should be designed as a single- or multiple-dose study with PK assessment of the parent drug and any active metabolites. In a multiple-dose study, PK assessment should be carried out on the first day, as well as at steady state. A single-dose study is satisfactory for cases where prior evidence indicates that multiple-dose PK is accurately predicted by single-dose data for both parent drug and active metabolites. This occurs when the drug and active metabolites exhibit linear and time-independent PK at the concentrations anticipated in the subjects to be studied. A multiple-dose study is desirable when the drug or an active metabolite is known to exhibit nonlinear or time-dependent PK. Although the planned clinical dose, as described in product labeling, should be used in the study, a reduced dose could be appropriate in patients with hepatic impairment if concern exists about the impairment causing toxicity due to increased blood levels of the drug.

3. Sample Collection and Analysis

The blood sampling period should be adequate to determine the terminal half-life of the drug and its active metabolites, with the expectation that these times could be extended in the patient compared to the control population. For drugs that are highly extracted by the liver (extraction ratio > 0.7) and that are extensively bound to plasma proteins (fraction unbound < 20 %), the unbound fraction should be determined at least at trough and maximum plasma concentration. The clearance and volume parameters should be expressed in terms of both unbound concentrations and total concentrations of drug in plasma and/or serum. Analytical methods should be sufficiently sensitive and specific to allow for analysis of the parent drug and its active metabolites. For drugs with stereochemical properties, stereoselectivity in drug metabolism and protein binding of enantiomers should be considered.³

B. Basic Full Study Design

³ FDA Policy Statement for the Development of New Stereoisomeric Drugs, May 1992.

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To make a labeling claim for appropriate dosing recommendations across the entire spectrum of hepatic impairment, the study should be conducted in control subjects and patients in the Child-Pugh categories of mild, moderate, and severe. A sufficient number of subjects should be enrolled in the study such that evaluable data can be obtained from at least six subjects in each arm of the study. The considerations outlined in section IV.A of this guidance should also be taken into account for this study design.

C. Population PK Approach

Population PK screening in phase 2 or 3 can be useful in assessing the impact on PK of covariates indicating altered hepatic function if these patients are not excluded from phase 2 or 3 trials and there is enough PK information collected about patients to characterize their impairment. If a population PK approach is to be used, patients in phase 2 or 3 studies should be assessed for encephalopathy, ascites, serum bilirubin, serum albumin, prothrombin time (components of the Child-Pugh score), or a similar group of measurements of hepatic function. A population PK study should include:

- ! Preplanned analysis of the effect of hepatic impairment
- ! Evaluation of the severity of liver disease
- ! A sufficient number of patients and a sufficient representation of the entire range of hepatic function to detect PK differences large enough to warrant dosage adjustment
- ! Measurement of unbound concentrations of the drug when appropriate
- ! Measurement of parent drug and active metabolites

These features are important if the sponsor intends to use the results to support a labeling claim that no dosage adjustment is required for patients with impaired hepatic function. For more detailed information about the design and execution of population PK studies, see the FDA guidance for industry on *Population Pharmacokinetics* (February 1999).

D. Pharmacodynamic Assessments

Pharmacodynamic assessments may be useful in studies designed to assess the effect of altered liver function, especially if concentration-response data are not available or if there is a concern that altered hepatic function could alter PD response. The selection of PD endpoints should be discussed with FDA review staff and should be based on the pharmacological characteristics of the drug and its active metabolites.

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V. DATA ANALYSIS

The primary intent of the data analysis is to assess the effect of hepatic impairment on the PK of a drug and its active metabolites and, if possible, to relate a specific measurement of hepatic function or group of functions (e.g., Child-Pugh) to a relevant PK measurement and/or parameter. From this information, dosage recommendations for patients with impaired hepatic function can be developed.

A. Parameter Estimation

Plasma concentration data (and urine concentration data, if collected) should be analyzed to estimate measurements and/or parameters describing the PK of the drug and its active metabolites (e.g., area under the plasma concentration curve (AUC), peak concentration (C_{max}), apparent clearance (CL/F), renal and nonrenal clearance (CL_R and CL_{NR}), apparent volume of distribution (Vd_z or Vd_{ss}), terminal half-life (t_{1/2})). Where relevant, measurements and/or parameters may be expressed in terms of unbound concentrations (e.g., apparent clearance relative to the unbound drug concentration (CL_u/F=Dose/AUC_u, where the subscript *u* indicates unbound drug)). Noncompartmental and/or compartmental modeling approaches to parameter estimates can be used.

B. Relationship Between Measurements of Hepatic Function and PK

Past experience indicates that clinically useful predictors relating some measurement or group of measurements of hepatic function to alterations in drug PK have not been as successful as approaches relating renal impairment to measurements and/or parameters of drug disposition. Using linear and nonlinear models, correlations can be sought between hepatic functional abnormality, measured for example by hepatic blood flow, serum albumin concentration, prothrombin time, or overall impairment scores such as Child-Pugh, and selected pharmacokinetic parameters (such as total body clearance, oral clearance, apparent volume of distribution, unbound clearance, or dose-normalized area under the unbound concentration-time curve). A regression approach for continuous variables for hepatic impairment and PK parameters is appropriate, with the understanding that some correlations will rely on categorical variables (e.g., Child-Pugh). If modeling is undertaken, results should include estimates of the parameters of the chosen model, as well as measurements of their precision (standard errors or confidence intervals). Prediction error estimates are also helpful in assessing the appropriateness of the model.

C. Development of Dosing Recommendations

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A general objective of a hepatic impairment study is to provide recommendations to patients and practitioners about changes in starting doses and dosing intervals in the presence of hepatic disease, with the understanding that subsequent careful titration could be needed in this vulnerable population. Depending on the outcome of a study, sponsors might wish to make labeling statements that hepatic impairment does not alter the PK of a drug. To assess such an outcome, a confidence interval approach is preferred to a significance test because these studies are comparative in nature.

A general approach to developing dosage recommendations could be based on the following considerations:

- If the effect of hepatic impairment on PK of the drug is obvious (e.g., twofold or greater increase), necessary dosage adjustments should be reflected in the labeling.
- If the sponsor wants to claim no effect of hepatic impairment on the drug's PK, then one of the following criteria should be established: (1) delineation of no effect boundaries prior to conducting the studies, based on information available for the investigational drug (e.g., dose- and/or concentration-response studies); (2) in the absence of other information to determine a different equivalence interval, a standard 90 percent confidence interval of 80-125 percent for AUC and 70-143 percent for C_{max} can be used for the investigational drug. Given the small numbers of subjects usually entered into hepatic impairment studies, FDA recognizes that documentation that a PK parameter remains within a certain no effect boundary at a certain level of confidence is unlikely.
- Because the general question is one of prescribability, a population equivalence criterion (not an individual equivalence criterion) could be useful to allow scaling to the variability of the PK measurement and/or parameter in the control study group. This criterion does not necessitate replicate study designs. Sponsors interested in this approach should consult with review staff at FDA.

VI. LABELING

The labeling should reflect data on the effect of hepatic impairment on the PK and PD (if known). Although drug characteristics and the effect of hepatic impairment on drug performance make it difficult to specify how such drugs should be labeled, drug dosage should be reduced if the clearance of the study drug is significantly impaired in moderate Child-Pugh hepatic impairment. Generally, a similar dosage reduction should be recommended for mild Child-Pugh hepatic impairment. Depending on the

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drug's use and therapeutic index, the drug may be contraindicated or used with great caution in severe Child-Pugh hepatic impairment.

Conversely, if the results show no significant impairment of drug clearance in the moderate group, the drug can be administered in the presence of mild and moderate hepatic impairment without any dose modification. Depending on the drug's use and therapeutic index, the labeling should generally indicate caution in severe hepatic impairment.

If a study is not conducted for the reasons listed in section III.B, the labeling should indicate that the impact of hepatic impairment has not been studied and that effects requiring a dosage adjustment are unlikely for the proposed drug.

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A. Clinical Pharmacology Section

1. Pharmacokinetics

Information in this section should include:

- ! Mechanism of hepatic elimination (enzyme pathways, glucuronidation, biliary excretion)
- ! Percent of drug eliminated by the liver
- ! Disposition of metabolites in patients with impaired hepatic function (if applicable)
- ! Effects of hepatic impairment on protein binding of parent drug and metabolites (if applicable)
- ! Effects of impaired hepatic function on stereospecific disposition of enantiomers of a racemic drug product, if there is evidence of differential stereoisomeric activity or toxicity

2. Special Populations

This section should briefly recapitulate the pharmacokinetic changes and should address any issues of altered PD and dosing adjustments for patients with hepatic impairment. This information should be based on studies performed in accordance with recommendations in this guidance or an acceptable alternative. Reference should be made to the WARNINGS, PRECAUTIONS, CONTRAINDICATIONS, and DOSAGE AND ADMINISTRATION sections. The following are examples of appropriate wording for the Special Populations section.

The simplest situation involves drugs for which studies of impaired hepatic function have been conducted and little or no effect on PK or PD was noted:

In a study comparing 8 patients with moderate hepatic impairment (as indicated by the Child-Pugh method) to 8 controls, the single- and/or multiple-dose PK/PD disposition of _____ was not altered in patients with hepatic impairment. No dosing adjustment is required in patients with mild and moderate hepatic impairment.

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For drugs whose PK or PD is influenced by hepatic impairment, the following statement can be modified, as appropriate, in accordance with what is known about the drug (e.g. racemate with different activity of stereoisomers, active or toxic metabolite) and from the studies performed in accordance with this guidance:

The disposition of _____ was compared in patients with hepatic impairment and people with normal hepatic function. Total body clearance of (unbound, if applicable) _____/metabolite was reduced in patients with impaired hepatic function by ____% in moderate hepatic impairment (as indicated by the Child-Pugh method). The half-life of _____/metabolite is prolonged by ____ in patients with moderate hepatic impairment. Protein binding of _____/metabolite is/is not affected by impaired hepatic function. The drug and/or metabolite accumulates to the extent of ____ in patients with impaired hepatic function on chronic administration. The dosage should be reduced in patients with mild and moderate hepatic impairment receiving _____. _____ should be contraindicated or used with great caution in severe hepatic impairment (see DOSAGE AND ADMINISTRATION).

In cases where no hepatically impaired patient population has been investigated as the basis for labeling claims, the following labeling language should be incorporated.

- (a) No hepatic contribution to the elimination of the compound:

The influence of hepatic impairment on the pharmacokinetics of _____ has not been evaluated. Because greater than 90% of the dose is excreted in the urine as unchanged drug, hepatic impairment would not be expected to have a significant effect on _____ elimination.

- (b) Limited (<20%) hepatic elimination:

- (i) Wide TI

The influence of hepatic impairment on the pharmacokinetics of _____ has not been evaluated. Because greater than 80% of the dose is excreted in the urine as unchanged drug, hepatic impairment is not expected to have a significant safety effect on blood levels of _____. In cases of concomitant renal failure, where there may be an increased role of hepatic elimination, patients with impaired liver function may require reduced initial and maintenance doses of _____ and/or

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longer dosing intervals compared to patients with normal hepatic function (see PRECAUTIONS).

(ii) Narrow TI

The influence of hepatic impairment on the pharmacokinetics of _____ has not been evaluated. Because the usual doses of the drug are close to doses that can cause adverse effects, and there is in vivo and/or in vitro evidence of hepatic contribution to the elimination of _____, hepatic impairment could lead to an increased rate of adverse effects. Patients with impaired liver function may require reduced initial and maintenance doses of _____ and/or longer dosing intervals compared to patients with normal hepatic function. In cases of concomitant renal failure, where there may be increased contribution of hepatic metabolism, _____ should, if possible, be avoided. If _____ is used, close monitoring of patients with impaired liver function is important.

(c) Extensive (> 20%) hepatic elimination:

(i) Wide TI

The influence of hepatic impairment on the pharmacokinetics of _____ has not been evaluated. Because there is in vitro and/or in vivo evidence of extensive hepatic contribution to the elimination of _____, hepatic impairment would be expected to have significant pharmacokinetic effects on _____. Caution should be exercised during the use of _____ in this patient population. Patients with impaired liver function would require reduced initial and maintenance doses of _____ and/or longer dosing intervals compared to patients with normal hepatic function (see PRECAUTIONS).

(ii) Narrow TI

The influence of hepatic impairment on the pharmacokinetics of _____ has not been evaluated. Because less than 20% of the dose is excreted in the urine as unchanged drug and there is in vitro and/or in vivo evidence of extensive hepatic contribution to the elimination of _____, hepatic impairment would be expected to have significant pharmacokinetic effects on _____. _____ should be contraindicated or used with great caution in this patient population (see CONTRAINDICATIONS).

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- (d) Hepatic elimination unknown:

In these circumstances, consider the compound as extensively metabolized and use the above format.

B. Precautions and/or Warnings Sections

If use in patients with impaired hepatic function results in clinically important changes in drug PK and/or PD, this should be included in the PRECAUTIONS section with reference to DOSAGE AND ADMINISTRATION. If a drug is known to have a narrow therapeutic index, consideration should be given to including a statement in the WARNINGS or CONTRAINDICATIONS section.

C. Dosage and Administration Section

As appropriate, the following statements should be included:

The influence of impaired hepatic function on _____ pharmacokinetics or pharmacodynamics (if known) is sufficiently small that no dosing adjustment is required.

For cases in which impaired hepatic function requires dosing adjustments, the appropriate information should be included.

Special consideration should be given to combination drug products. It is reasonable to recommend dosing adjustment according to the degree of hepatic impairment if there is sufficient information to indicate that the pharmacokinetics of the individual components are similarly affected by impaired hepatic function. For situations in which this does not apply, the following statement should be adapted:

Because the doses of this fixed combination product cannot be individually titrated and impaired hepatic function results in a reduced clearance of component A to a much greater extent than component B, combination product should generally be avoided in patients with impaired hepatic function (see WARNINGS or PRECAUTIONS, as appropriate).

In some cases, where various ratios of the combination product are available, it may be possible to direct physicians to a combination with less of the hepatically cleared component.

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APPENDIX: ASSESSMENT OF LIVER FUNCTION.

1. Child-Pugh System

	Points Scored for Observed Findings		
	1	2	3
Encephalopathy grade*	none	1 or 2	3 or 4
Ascites	absent	slight	moderate
Serum bilirubin, mg/dL	<2	2 to 3	>3
Serum albumin, g/dL	>3.5	2.8 to 3.5	<2.8
Prothrombin time, sec prolonged	<4	4 to 6	>6

*Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity

Assessment as good operative risk (A) if 5 or 6 points; moderate risk (B) if 7 to 9 points, and poor operative risk (C) if 10 to 15 points (developed for surgical evaluation of alcoholic cirrhotics)

2. Maddrey Discriminant Function (df)

$$df = 4.6 \times (\text{prothrombin time, in seconds}) + \text{serum total bilirubin, mg/dL}$$

Interpretation of the df values in patients with acute alcoholic hepatitis was that the disease was not severe if df <54, was severe if 55 to 92, and probably lethal if 93 or more if untreated.

The df was modified in a later study by Carithers et al., to use the prolongation of prothrombin time above normal control values and to divide the serum bilirubin by 17.1 to give mmol/L. Patients with modified df values of 32 or more were entered into study of methylprednisolone treatment, corresponding to Maddrey df values of approximately 106.

3. Mayo Survival Model for Primary Biliary Cirrhosis

This model, based on Cox proportional hazards regression analyses for factors predicting death, used

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the five most influential variables in a complex formula to calculate estimated survival time, $S(t)$, in terms of mortality risk, R :

$$S(t), \text{ survival probability for } t \text{ years} = \{S_0(t)\}^{\exp(R-5.07)}, \text{ where}$$
$$R = 0.871 \ln(B) + 2.53 \ln(A) + 0.039(Y) + 0.859(E) + 2.38 \ln(PT).$$

[B=bilirubin, mg/dL; A=albumin, g/dL; Y=age in years; E=edema; PT=prothrombin time, sec]

$S_0(t)$ is taken from a table of observed survivals for $R=5.07$, the mean value of risk score found in the 418 patients observed:

t, years	1	2	3	4	5	6	7
$S_0(t)$	0.970	0.941	0.883	0.833	0.774	0.721	0.651

Later the same year, another model was developed for 174 patients with primary sclerosing cholangitis (PSC) by Wiesner and colleagues at the same institution, but the regression analysis identified blood hemoglobin (Hb, g/dL, below 12 g/dL), inflammatory bowel disease (IBD: 1 if yes, 0 if no), and the histological stage of hepatic fibrosis (S, 0 to 4) as important, in addition to age and serum bilirubin (up to 10 mg/dL used if observed value higher):

$$R = 0.85 \ln(B) + 0.06(Y) - 4.39 \ln(Hb) + 1.59(IBD) + 0.51 S$$

4. Monoethylglycinexylidide (MEGX)

This compound is the main metabolite of lidocaine, produced by oxidative N-de-ethylation by the hepatic CYP3A enzyme system. It is measured at 15, 30, or 60 minutes after an intravenous infusion over 2 minutes of 1 mg/kg of lidocaine, and correlates well with Child-Pugh scores (Testa et al., 1997).

5. Galactose Single Point (GSP) Method

A simplification (Tang and Hu, 1992) of the older, more tedious galactose elimination constant (GEC) developed by Tygstrup in 1963 has been validated in patients with chronic hepatitis and cirrhosis graded by the Child-Pugh scale and GEC. The test is done by intravenously infusing 0.5 g/kg of galactose, and measuring serum galactose concentration enzymatically at 60 minutes later. Elevated blood galactose correlates sensitively with hepatic dysfunction. There is some evidence that the GSP test can be used to define clearance of both highly metabolized drugs and drugs that are hepatically excreted but not

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metabolized.